REVIEW ARTICLE

# An Effective but Forgotten Therapy in Dysmenorrhea

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## Abstract

Dysmenorrhea has no long-lasting therapeutic strategy despite the advances in medicine. The European medicinal plants such as *Valeriana officinalis*, *Passiflora incarnata* and *Humulus lupulus* have been used as folklore remedy in the past century. However, they have not reached the masses due to paucity of information in the leading medical journals. This article reviews the clinical benefits and possible mechanism of action of these medicinal plants in the treatment of dysmenorrhea. We also suggest this fixed dose combination in the management of dysmenorrhea in daily clinical practice.

**Keywords:** Dysmenorrhea, *Humulus*, *Passiflora*, Valerian.

*Journal of South Asian Federation of Obstetrics and Gynaecology* (2019): 10.5005/jp-journals-10006-1683

## Introduction

Dysmenorrhea is an inescapable complaint in many women across the globe. Dysmenorrhea is common from menarche to 25 years causing severe and disabling pain. Often, women with dysmenorrhea have poor quality of life and leads to absenteeism from work. Around 60% of reproductive age women report pain during menstruation. Despite the latest advances in the treatment, more than half of women with dysmenorrhea continue to have symptom during every cycle of menstruation. Due to persistence of severe to moderate pain even after treatment, more than half of women continue to have limitation of day to day activities. Excessive amount of prostanoids and eicosanoids released from the endometrium during menstruation are implicated in the pathophysiology of dysmenorrhea. There is increased prostaglandin synthesis that leads to uterine contractions and vasoconstriction during menstruation. Frequent and dysrhythmic contractions are also associated with increased basal tone and active pressure. Uterine hyper contractility, reduced uterine blood flow, and peripheral nerve hypersensitivity occur at the time when maximal prostaglandins are released into the menstrual fluid (Fig. 1). Prostaglandin E2, has been shown to increase psychological stress and impair memory.[1] Hence, it is imperative to include medications that are centrally acting to control these symptoms.

In addition, vasopressin levels have been found to be elevated in women with primary dysmenorrhea. Vasopressin increases uterine contractility and causes ischemic pain as a result of vasoconstriction. In primary dysmenorrhea menstrual cramps occur without pelvic abnormalities while in secondary dysmenorrhea the same occurs due to reproductive organ disorders such as endometriosis, adenomyosis and fibroid. A common early clinical symptom of endometriosis is a clinical history of dysmenorrhea, which is often primary and severe. Failure of treatment with NSAIDs is not uncommon. Such individuals are treated with oral contraceptives (OC).[2] Suppressing ovarian function with OC improves the symptoms of primary dysmenorrhea, but these classically recur upon cessation of OC. Endometriosis and OC use are linked.[3,4] In a case-control study, (Parazzini) reported high risk of endometriosis associated with OC use.[5] Approximately 30–50% was reported infertility among patients with endometriosis in an Italian study. The link between primary dysmenorrhea and infertility might seem distant but is quite substantiated.[6]

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**How to cite this article:** Gomathy N, Dhanasekar KR, Trayambak D. An Effective but Forgotten Therapy in Dysmenorrhea. J South Asian Feder Obst Gynae 2019;11(3):203–206.

**Source of support:** Nil

**Conflict of interest:** None

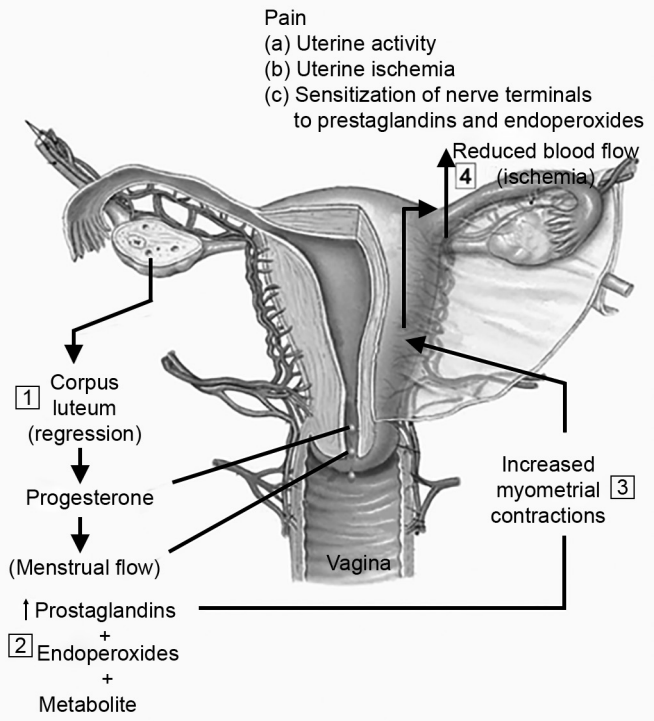



**Fig. 1:** Pathogenesis of dysmenorrhea

Nonsteroidal anti-inflammatory drugs (NSAIDs) such as mefenamic acid is the mainstay of treatment of dysmenorrhea. Though NSAIDs improve the symptoms, the benefits are not long-lasting. The pain recurs during every cycle. If mefenamic acid is used for a longer duration, it causes heart burn, constipation, nephro-toxicity, hemolytic anemia, seizures and diarrhea. However, many women are forced to consume NSAIDs despite the adverse effects such as gastric irritation, gastric ulceration, heart burn, drowsiness and diarrhea. Prostaglandins play an essential role in ovulation and NSAIDs such as meloxicam and COX-2 inhibitors are reported to delay ovulation due to inhibition of prostaglandins.[7,8]

Therefore, there is a need for alternative and effective therapy which is devoid of the above-mentioned adverse effects. It is also preferred to administer medications that do not alter the menstrual cycle or delay ovulation. In this context, clinicians can choose herbal extracts that have proven benefit in dysmenorrhea and may be a safer alternative but as effective as NSAID.

Herbal treatment modalities were found to be as effective as mefenamic acid in pain management in primary dysmenorrhea. Although NSAIDs are the mainstay of treatment of pain in dysmenorrhea, a clinical study done with ginger was as effective as mefenamic acid in controlling the severity of dysmenorrhea, duration of pain, cycle duration and volume of bleeding.[9] Notably, there were no adverse effects reported in the ginger group. Hence, the role of herbal extracts is gaining significance and alternative therapy for dysmenorrhea is emerging.

In this review, we selected herbs that have spasmolytic, anxiolytic, and anti-inflammatory action. Medicinal plant extracts from *Valeriana officinalis*, *Passiflora incarnata* and *Humulus lupulus*, either in combination or as a single ingredient have the above-mentioned properties. This review suggests an alternative safe and effective strategy to control the symptoms of dysmenorrhea.

## Herbal Extracts for the Treatment of Dysmenorrhea

### *Valerian in Dysmenorrhea*

*Valeriana officinalis* (known as valerian) is a bushy plant whose roots and rhizomes have been used since 10th century for its beneficial effects in painful menstruation. The active pharmaceutical ingredient (API) in valerian is valerenic acid which inhibits contraction of smooth muscles resulting from cellular depolarization.

Both *in vivo* and *in vitro* studies have shown its antispasmodic activity on smooth muscles (Hazelhoff, 1982). As per this study valerian was found to be equipotent to papaverine in inhibiting smooth muscle contractions. Valerian relaxed smooth muscle cells by acting as a musculotropic agent. Valerian has been widely used for reducing pain, cyclic cramps, dysmenorrhea, anxiety, and stress. There were no adverse effects, or hypersensitivities reported in clinical studies, and it is safe to use during pregnancy and breastfeeding. It is classified as a safe drug, and Food and Drug Administration puts no restriction on its import as a food supplement. Varied dose of valerian has been used. In one such study, 255 mg of valerian was administered amongst 49 patients, 3 times daily for 2 days at the onset of menstruation for 2 consecutive menstrual cycles. In this study the systemic manifestations associated with dysmenorrhea decreased significantly after the intervention. The possible mechanism is that valerian inhibited contractions resulting from cellular depolarization.[10] As per the systematic review, valerian was significantly better in reducing pain as compared to placebo group.

It is noteworthy that valerian opens potassium channels and blocks calcium channels. When potassium channels open, the intracellular calcium concentration decreases, which in turn relaxes uterine muscle.[11] Figure 2 represents the mechanism of action of valerian via binding to $GABA_A$ receptor.

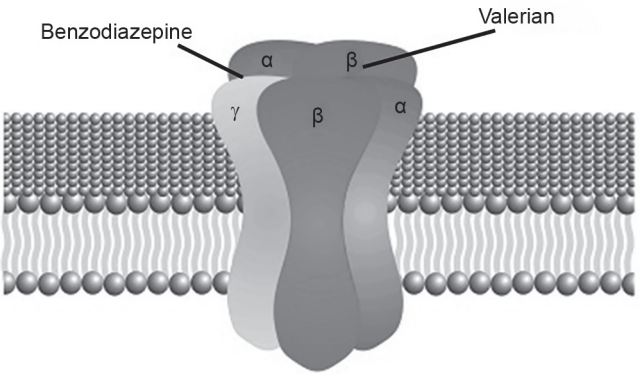



**Fig. 2:** Mechanism of action on *Valeriana officinalis* in dysmenorrhea

Sub-chronic toxicological studies have shown that, the maximum tolerable dosage of *Valeriana officinalis* is 2,790 mg/kg/day. In humans, valerian overdosage leads to CNS depression, cardiac disorders, headache, mydriasis, restless states and sleeplessness.[12] Higher dose of valerian (900 mg) was reported to have increased sleepiness amongst patients, but there was no death reported at this dose. It seems that valerian has a wide therapeutic window. Therefore, a wide dose range can be prescribed for various groups of women. *Valeriana officinalis* and mefenamic acid were compared head on in reduction of pain score in primary dysmenorrhea. A randomized controlled clinical trial enrolled 39 patients aged between 16 and 42 years diagnosed with primary dysmenorrhea. A total of 18 patients in the intervention group took 350 mg *valerian* three times a day, and in mefenamic group, 21 patients took 250 mg mefenamic acid three times a day for three days for three cycles, starting from the onset of bleeding or pain. Post intervention, findings of the study revealed statistically significant reductions in mean of pain score in *Valeriana officinalis* ($p < 0.001$). In this study, the mean pain score reduced equally in both *Valeriana officinalis* and mefenamic acid groups. In addition, fewer side effects were noted in the *Valeriana officinalis* group when compared with mefenamic acid group. Hence, it can be stated that valerian is non inferior to mefenamic acid in pain reduction with a better safety profile.[13] From the available studies, it appears that the effective dose of valerian at a dose of 300 mg will be a potent analgesic and spasmolytic especially in menstrual associated cramps or pain. Valerian is also known to be effective in the treatment of spasms associated with diarrhea, intestinal colic, and irritable bowel syndrome.[14]

### *Passion Flower in Dysmenorrhea*

*Passiflora incarnata* (known as passion flower) has been used since ages as a sedative in North America and as an analgesic, antispasmodic, antiasthmatic and wormicidal in Brazil. It has been used for dysmenorrhea, epilepsy, insomnia and neurosis in Turkey. *Passiflora incarnata* is a woody vine, 10 m in length and has tendrils which are employed to climb over other plants in the forest. The main constituents of passion flower leaves are flavonoid (0.25%) such as vitexin, (the active pharmaceutical ingredient), isovitexin, orientin, isoorientin, apigenin and kampferol. Besides flavonoids, various indole alkaloids based on β-carboline ring system are present, which include harman, harmine, harmalol

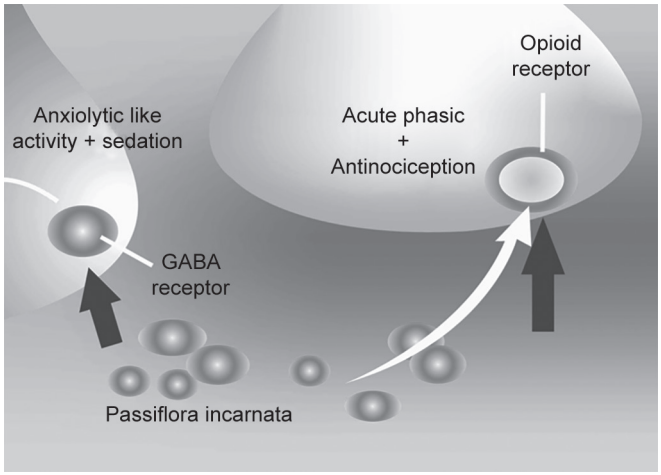
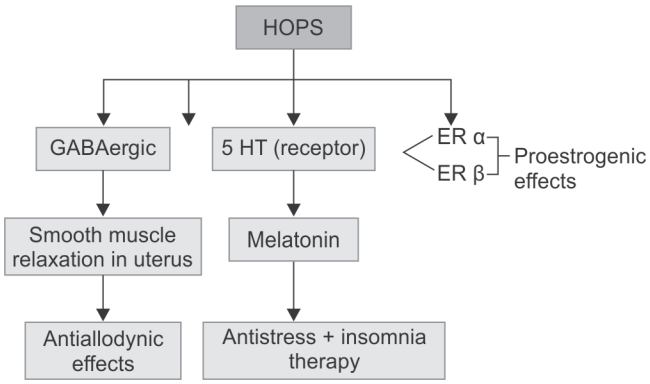



**Fig. 3:** Mechanism of action of *Passiflora incarnata* in dysmenorrhea

**Flowchart 1:** Mechanism of action on *Humulus lupulus* in dysmenorrhea




and harmaline. Various other phytoconstituents present in passion flower include carbohydrates, essential oil, amino acids and a cyanogenic glycoside gynocardin. It has been known to possess anxiolytic, sedative-hypnotic, anticonvulsant, anti-inflammatory, antitussive, antiasthmatic and aphrodisiac activity. The traditional claims about *Passiflora incarnata* suggest its potential as analgesic and an important treatment for neuralgia.

Passion flower mainly acts on the central nervous system. It increases the levels of inhibitory gamma-aminobutyric acid (GABA) in the brain. Figure 3 illustrates the mechanism in the CNS synaptic cleft. GABA decreases the brain activity thereby relaxing the patient. *Passiflora incarnata* has proven to be a potent anxiolytic over ages. In a study amongst 36 patients with generalized anxiety disorder, it was found to be as effective as the current benzodiazepine, oxazepam.[15] In another study 99 patients who were screened for anxiety symptoms, it was found that *Passiflora incarnata* along with other herbs effectively controlled the symptoms as compared to placebo group. Passiflora extract was evaluated in an animal study where in it was found to have dose dependent naloxone and pentylenetetrazol reversible antinociception suggesting an involvement of opioidergic and GABAergic mechanisms.[16] In streptozotocin-induced neuropathic nociceptive model, *Passiflora incarnata* at a dosage of 200 mg exhibited dynamic and static antiallodynic effects substantiated by an increase in paw withdrawal threshold and paw withdrawal latency. The rearing incidence was reduced by *Passiflora incarnata* at all the tested doses and it decreased locomotor activity to an extent which was analogous to diazepam in open field test. The antiallodynic effect of *Passiflora incarnata* is well established in dysmenorrhea.[17]

Another study (Ingale, 2012) reported 150 mg of *Passiflora incarnata* to analgesic effect. In the hot plate test and abdominal constriction assay, *Passiflora incarnata* produced dose dependent, naloxone and pentylenetetrazole reversible antinociception suggesting an involvement of opioidergic and GABAergic mechanisms. In the stair case test, *Passiflora incarnata* at 200 mg/kg increased the number of steps climbed. The role of Passiflora is well established as an analgesic and anti-inflammatory agent. The dose 200 mg/kg of Passiflora extract exhibited analgesic activity [(13.50 ± 0.43) minutes] *p* value < 0.01, at a reaction time of 20 minutes in hot plate method. The extract at a dose of 100 mg/kg produced a highly significant anti-inflammatory effect [(1.302 ± 0.079) mL, *p* value < 0.01.[18]

### *HOPS in Dysmenorrhea*

*Humulus lupulus* (known as HOPS) is an herb which grows in Asia, America and Europe. It has been majorly employed to treat insomnia, restlessness, nervousness and impulsiveness. The analgesic and antianxiety effects of HOPS have been widely mentioned in various pharmacopoeias around the world.

HOPS mainly constitutes of flavonoids, terpenophenolics and phenolic acids. It has an active principle named rutin. Apart from alpha acids present in HOPS, rutin also plays an important role in exhibiting its antianxiety effect. The mechanism of action of HOPS in exercising analgesic action on uterine smooth muscle is via the inhibition of central nervous cholinergic system.[19] The GABAergic arm of Flowchart 1 demonstrates the mechanism of Hops in pain management of dysmenorrhea.[20] Isohumolone is isolated from hops extract as the active principle and it is found to have analgesic effect.[21] Isohumolones are effective in reducing inflammatory arthritis pain in clinical trials based on improvement in WOMAC score.[22,23]

The recommended dosage for *Humulus lupulus* to achieve analgesia is 100 mg/day. The lethal dose for HOPS is 3500 mg/kg body weight for oral formulations. Muscle relaxation can be due to competitive inhibition on acetylcholine induced contractions. The smooth muscle relaxant effect may also be induced by stimulating the nitric oxide, purinergic or adrenergic modulatory systems. GABA receptors have been found in intestine, ovaries, testis and uterine smooth muscles. HOPS has GABAergic properties and leads to uterine smooth muscle relaxation in dysmenorrhea.[19]

## Conclusion

We have found clinical evidences that herbal extracts of valerian, passion flower and hops can have significant therapeutic role in dysmenorrhea. Our analysis of literature points to a synergistic pharmacological action of these three ingredients in dysmenorrhea. The herbal extracts have dual mode of action both in the uterus and in the brain. Owing to the synergistic action, extracts of valerian, passion flower and hops can reduce pain, anxiety and the associated psychological stress due to dysmenorrhea. As per the available literature, fixed dose combination of 300 mg valerian extract, 80 mg passion flower extract and 30 mg hops extract can be used in the management of dysmenorrhea in daily clinical practice. We also suggest the above-mentioned fixed dose combination be

studied in a well-designed randomized controlled trial to establish the long-term clinical efficacy in dysmenorrhea.

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